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(54) Title: METHODS OF TREATING ANXIETY DISORDERS

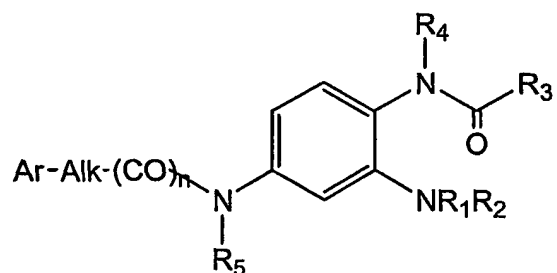
(57) Abstract: This invention provides methods for treating, preventing or inhibiting anxiety, anxiety-related conditions and phobias in a mammal using compounds of the formula (I) wherein: R₁ is H, alkyl, alkanoyl or the radical Ar; R₂ is H or alkyl; R₃ is alkoxy, NH₂, alkylamino, dialkylamino, amino substituted by the radical Ar, alkyl, alkenyl, alkynyl, or the radicals Ar or ArO-; R₄ is H, alkyl or the radical Ar; R₅ is H or alkyl or the radical Ar; or a pharmaceutically acceptable salt or ester form thereof; Ar is an optionally substituted phenyl radical; and n is 0 or 1, or a pharmaceutically acceptable salt or ester form thereof, with the methods particularly including the use of N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester, also known as retigabine.

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METHODS OF TREATING ANXIETY DISORDERS

This invention relates to novel methods for treating, preventing or inhibiting anxiety and anxiety-related conditions in a mammal, preferably in a human. The methods of this invention include the treatment, prevention, inhibition and amelioration of conditions including anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, post-traumatic stress disorder, agoraphobia and specific phobias.

- 10 U.S. Patent No. 5,384,330 (Dieter et al.) teaches pharmacologically active 1,2,4-triaminobenzene derivatives of the General Formula:



and their properties as anti-epileptic, muscle relaxing, fever-reducing and peripheral analgesic agents.

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U.S. Patent No. 5,849,789 and 5,852,053 (both to Rostock et al.) teaches the use of retigabine for the treatment of neurodegenerative disorders, including those associated with stroke.

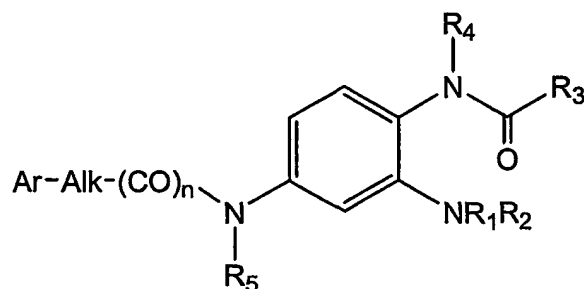
- 20 U.S. Patent No. 5,914,425 (Meisel et al.) teaches novel crystalline forms of retigabine.

- 25 U.S. Patent No. 6,117,900 teaches the use of retigabine, also known as N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester, for the treatment of neuropathic pain.

Description of the Invention

This invention provides methods for treating anxiety disorders and anxiety-related conditions in a mammal, preferably including methods for such treatment in humans.

Among the compounds useful in the methods of this invention are those disclosed in U.S. Patent No. 5,384,330 (Dieter et al.) the contents of which are incorporated herein by reference. The compounds include those of the formula:



wherein:

R₁ is selected from hydrogen, C₁—C₆-alkyl, C₂—C₆-alkanoyl or the radical Ar;

R₂ is selected from hydrogen or C₁—C₆-alkyl;

R₃ is selected from C₁—C₆-alkoxy, NH₂, C₁—C₆-alkylamino, C₁—C₆-dialkylamino, amino substituted by the radical Ar, C₁—C₆-alkyl, C₂—C₆-alkenyl, C₂—C₆-alkynyl, the radical Ar or the radical ArO-;

R₄ is selected from hydrogen, C₁—C₆-alkyl or the radical Ar;

R₅ is selected from hydrogen or C₁—C₆-alkyl or the radical Ar;

Alk indicates a straight or branched alkylene group with 1-9 carbon atoms, which can also be substituted by the radical Ar;

Ar is a phenyl radical substituted by the radicals R₆, R₇ and/or R₈ where these radicals R₆, R₇ and R₈ are the same or different and represent H, C₁—C₆-alkyl, C₃—

C₇-cycloalkyl, hydroxy, C₁-C₆-alkoxy, C₂-C₆-alkanoyloxy, halogen, hydroxy, C₁-C₆-halogenoalkyl, -CN, -NH₂, -NH-C₁-C₆-alkyl, -N(C₁-C₆-alkyl)₂, -CO₂H, -CO-C₁-C₆-alkyl, -CO-O-C₁-C₆-alkyl, -COAr, -CO-OAr, -CONH₂, -CONH-C₁-C₆-alkyl, -CON(C₁-C₆-alkyl)₂, -CONHAr, -NH-CO-C₁-C₆-alkyl, -NHCO-Ar, -NHCO-C₁-C₆-alkoxy, -N-H-CO-Ar, -NHCO-NH₂, -NHCO-N(C₁-C₆-alkyl)₂, -NHCO-NHAr, -NH-SO₂-C-1-C₆-alkyl, -NH-SO₂Ar, -NH-SO₂-nitrophenyl, -SO₂-OH, -SO₂-C₁-C₆-alkyl, -SO₂-Ar, -SO₂-C₁-C₆-alkoxy, -SO₂-OAr, -SO₂-NH₂, -SO₂-NH-C₁-C₆-alkyl, -SO₂-N(C₁-C₆-alkyl)₂, -SO₂-NHAr, -SO₂-C₁-C₆-alkoxy;

10 n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

The alkyl groups, halogenalkyl groups, alkenyl groups, alkynyl groups, alkoxy groups, alkylamino groups, alkanoyl amino groups, alkanoyloxy groups and alkanoyl groups in general can be straight or branched. The same also applies to alkyl and alkyloxy groups (=alkoxy groups) if these are components of more complicated radicals for example in the form of a monoalkyl- or dialkylamino group, alkanoylamino group, carbalkoxy group, alkylcarbonyl group and analogous groups. The C₃-C₇-cycloalkyl group is preferably cyclopentyl or cyclohexyl. C₂-C₆-alkenyl preferably represents allyl. C₂-C₆-alkynyl preferably represents propargyl.

The halogen atoms are chlorine, bromine or fluorine, in particular chlorine or fluorine. The alkyl and alkoxy groups as such or as components of groups of more complicated radicals consist in particular of 1-4 carbon atoms, preferably 1 or 2 carbon atoms. Alkanoyl groups, such as alkanoylamino groups or alkanoyloxy groups consist in particular of 2-4, preferably 2-3 carbon atoms. Alk consists in particular of 1-3, preferably 1 or 2 carbon atoms.

Among the more preferred compounds of this group are:

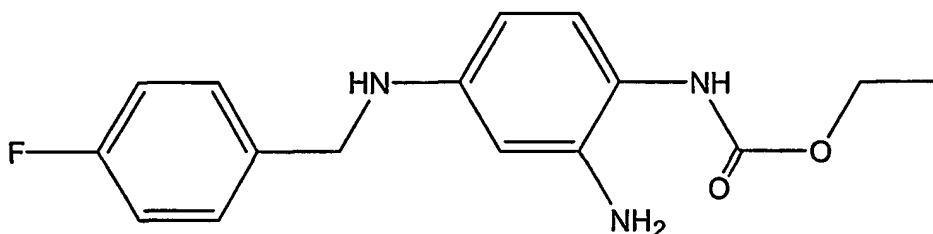
- 30 2-Amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino benzene;
- 2-Amino-4-(4-trifluoromethylbenzylamino)-1-ethoxycarbonylamino-benzene;
- 2-Amino-4-benzylamino-1-ethoxycarbonylamino-benzene;
- 2-Amino-4-(3,5-dichlorobenzylamino)-1-ethoxycarbonylamino benzene;

2-Amino-4-(3,5-dichlorobenzylamino)-1-propyloxycarbonylamino benzene;
 2-Amino-(2-chlorobenzylamino)-1-(diethylcarbamoylamino) benzene;
 2-Amino-4-(2,4-dichlorobenzylamino)-1-(dimethylcarbamoylamino) benzene;

and

5 1,2-Diacetylamino-4-(4-fluorobenzylamino) benzene; each of which can be prepared as described in U.S. Patent No. 5,384,330.

Among the most preferred compounds for use in the methods of this invention are N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid and its
 10 pharmaceutically acceptable salts and ester forms. Of particular preference is retigabine, also known as N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester (CAS Registry No. 150812-12-7), having the formula:



15 Also useful in the methods of this invention are the metabolite forms of retigabine which may be isolated from blood, urine or feces of recipients of N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester. The metabolites include the glucoside of retigabine, [4-(4-Fluoro-benzylamino)-2-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydropyran-2-ylamino)-phenyl]-carbamic acid ethyl ester, as well
 20 as its two glucuronide analogs, 6-[2-Ethoxycarbonylamino-5-(4-fluoro-benzylamino)-phenylamino]-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid and 6-[(3-Amino-4-ethoxycarbonylamino-phenyl)-(4-fluoro-benzyl)amino]-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid. Further metabolites include N-[2-Amino-4-(4-fluoro-benzyl-
 25 amino)phenyl]acetamide, its cyclized analog (4-Fluoro-benzyl)-2-methyl-1H-benzimidazol-5-yl)amine and the glucuronide analogs of N-[2-Amino-4-(4-fluoro-benzyl-amino)phenyl]acetamide, 6-[(4-Acetylamino-3-amino-phenyl)-(4-fluoro-benzyl)-amino]-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid and 6-[2-Acetylamino-5-(4-fluoro-benzylamino)-phenylamino]-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid.

The applications may utilize conventional oral, rectal, parenteral or intravenous delivery methods as conventionally utilized in medical or veterinary practice. Most preferable in most instance for home use are oral tablets or capsules
5 or neat compound or powdered or granular pharmaceutical formulations which may be mixed with chewable or liquid formulations or food materials or liquids acceptable to the recipient.

The methods of this invention include the treatment, prevention, inhibition and
10 amelioration of conditions in mammals in need thereof including anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia and specific phobias. Such mammals may be those presently
15 experiencing the anxiety-related symptoms or conditions of these disorders or those subject to such occurrences. Specific anxiety related phobias which may be treated with these methods are those commonly experienced in clinical practice including, but not limited to, fear of animals, insects, storms, driving, flying, heights or crossing bridges, closed or narrow spaces, water; blood or injury, as well as extreme fear of
20 inoculations or other invasive medical or dental procedures.

The methods for treating, preventing, inhibiting or ameliorating the maladies listed above or their symptoms comprise administering to a mammal in need thereof a pharmaceutically effective amount of a compound of this invention. A particular
25 method of treating, preventing, inhibiting or ameliorating the maladies in question comprises administering to the mammal in need of such assistance a pharmaceutically or therapeutically effective amount of N-[2-amino-4-(4-fluorobenzyl-amino)-phenyl]carbamic acid or a pharmaceutically acceptable salt or ester form thereof. Particularly included in these methods is the use of N-[2-amino-4-(4-
30 fluorobenzylamino)-phenyl]carbamic acid ethyl ester, also known as retigabine, or a pharmaceutically acceptable salt form thereof.

As used herein, the terms "pharmaceutically effective amount" or "therapeutically effective amount" mean the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, prevention, amelioration, or a decrease in the frequency of the anxiety or anxiety-related condition or symptoms in question. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

10

The methods of this invention may be accomplished with a daily dose of the active compounds described above of from about 0.1 mg/kg to about 30 mg/kg. Doses may be administered as a single regimen or as a continuous regimen divided by two or more doses over the course of a day.

15

Human administration may be at dosages of from about 10 mg BID to about 1000 mg BID, preferably from about 50 mg BID to about 500 mg BID, more preferably at a dose of from about 100 mg BID to about 300 mg BID.

20

Compounds as described in U.S. Patent No. 5,384,330, including retigabine, can be administered orally using conventional pharmaceutical excipients or carriers, preferably coated or contained in hard or soft gelatin capsules. Examples of oral formulations contained in hard gelatin capsules can include those in which the active compound comprises from about 45% to 50%, by weight, of the formulation. Microcrystalline cellulose comprises from about 43% to about 47%, povidone comprises from about 3% to about 4%, and silicon dioxide and magnesium stearate each comprise from about 0.3% to about 0.7%, each by weight. Specific examples of capsules containing 50 mg, 100 mg and 200 mg may be formulated utilizing the following lists of components.

25
30

50 mg Retigabine Capsules

| | <u>Ingredient</u> | <u>Amount/Capsule</u> |
|----|---|-----------------------|
| 5 | Retigabine | 50.0 mg |
| | Microcrystalline Cellulose, NF | 45.5 mg |
| | Povidone, USP | 3.5 mg |
| | Silicon Dioxide, Colloidal, anhydrous, NF | 0.5 mg |
| | Magnesium Stearate, EP | 0.5 mg |
| 10 | Theoretical Fill Weight | 100 mg |

100 mg Retigabine Capsules

| | <u>Ingredient</u> | <u>Amount/Capsule</u> |
|----|---|-----------------------|
| 15 | Retigabine | 100.0 mg |
| | Microcrystalline Cellulose, NF | 91.0 mg |
| | Povidone, USP | 7.0 mg |
| | Silicon Dioxide, Colloidal, anhydrous, NF | 1.0 mg |
| | Magnesium Stearate, EP | 1.0 mg |
| 20 | Theoretical Fill Weight | 200 mg |

200 mg Retigabine Capsules

| | <u>Ingredient</u> | <u>Amount/Capsule</u> |
|----|---|-----------------------|
| 25 | Retigabine | 200.0 mg |
| | Microcrystalline Cellulose, NF | 182.0 mg |
| | Povidone, USP | 14.0 mg |
| | Silicon Dioxide, Colloidal, anhydrous, NF | 2.0 mg |
| | Magnesium Stearate, EP | 2.0 mg |
| 30 | Theoretical Fill Weight | 400 mg |

The ingredients in the formulations above can be prepared using the following steps.

35 1) Weigh separately the active ingredient (retigabine), preferably screened through an 800 micron screen, and the microcrystalline cellulose components.

40 2) Prepare a granulation solution by dissolving the Povidone, USP in purified water.

- 3) Place the ingredients from Step 1 into a suitable blender and mix thoroughly.
- 5 4) Screen the mixture from Step 3 through a 1000 μm screen and place the screened mixture into the vessel of a fluidized bed granulator.
- 5) Heat the ingredients in the fluid bed granulator up to 27°C product temperature while mixing.
- 10 6) Add the granulation solution from Step 2 to the fluid bed.
- 7) Dry the granulate in the fluid bed.
- 15 8) Weigh the colloidal silicon dioxide component, preferably screened through a 1000 μm screen, and the magnesium stearate component, preferably screened through a 600 μm screen.
- 9) Add the silicon dioxide and magnesium stearate components to the
20 fluid bed granulator's vessel containing the dried granulate from Step 7 and mix the components thoroughly.
- 10) Screen the mixed components from Step 9, preferably through a 800
25 μm screen.
- 11) Transfer the final screened components into a suitable blender and mix thoroughly.

30 The final component mixture from Step 11 can then be coated, encapsulated or compressed into tablets utilizing conventional tablet excipients or carriers, as desired. It will be understood that oral dosage forms within the scope of this invention can be prepared using the components listed above in respective amounts according the dose of active ingredient in the particular formulation. For veterinary

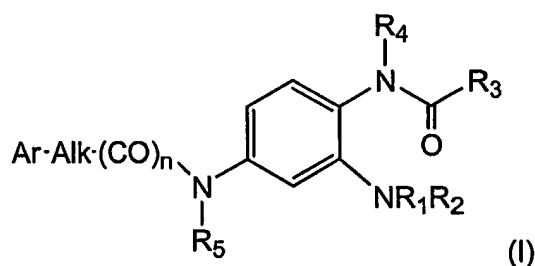
uses, the final mixture of Step 11 can be administered neat or mixed into foods acceptable to the animal in question. Further, the mixtures can be formulated into tablets, capsules or coated products, as described above, or integrated into conventional veterinary medicaments or food products.

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For intravenous administration, the compounds described herein may be prepared and maintained in conventional lyophilized formulations and reconstituted prior to administration with an intravenously acceptable saline solution, such as a 0.9% saline solution. The pH of the intravenous formulation can be adjusted, as
10 needed, with an intravenous and pharmaceutically acceptable acid, such as methanesulfonic acid.

CLAIMS

1. A method of treating or inhibiting anxiety disorders in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formula (I):



wherein:

- R₁ is selected from hydrogen, C₁—C₆-alkyl, C₂—C₆-alkanoyl or the radical Ar;
 R₂ is selected from hydrogen or C₁—C₆-alkyl;
- 10 R₃ is selected from C₁—C₆-alkoxy, NH₂, C₁—C₆-alkylamino, C₁—C₆-dialkylamino, amino substituted by the radical Ar, C₁—C₆-alkyl, C₂—C₆-alkenyl, C₂—C₆-alkynyl, the radical Ar or the radical ArO-;
- R₄ is selected from hydrogen, C₁—C₆-alkyl or the radical Ar;
 R₅ is selected from hydrogen or C₁—C₆-alkyl or the radical Ar; Alk: a straight or
- 15 branched alkylene group with 1-6 carbon atoms, which can also be substituted by the radical Ar;
- Ar is a phenyl radical substituted by the radicals R₆, R₇ and/or R₈ where these radicals R₆, R₇ and R₈ are the same or different and represent C₁—C₆-alkyl, C₃—C₇-cycloalkyl, hydroxy, C₁—C₆-alkoxy, C₂—C₆-alkanoyloxy, halogen, hydroxy, C₁—C₆-
- 20 halogenoalkyl, -CN, -NH₂, -NH—C₁—C₆-alkyl, -N(C₁—C₆-alkyl)₂, -CO₂H, -CO—C₁—C₆-alkyl, -CO—O—C₁—C₆-alkyl, -COAr, -CO—OAr, -CONH₂, -CONH—C₁—C₆-alkyl, -CON(C₁—C₆-alkyl)₂, -CONHAr, -NH—CO—C₁—C₆-alkyl, -NHCO—Ar, -NHCO—C₁—C₆-alkoxy, -N—H—CO—Ar, -NHCO—NH₂, -NHCO—N(C₁—C₆-alkyl)₂, -NHCO—NHAr, -NH—SO₂—C₁—C₆-alkyl, -NH—SO₂Ar, -NH—SO₂-nitrophenyl,
- 25 -SO₂—OH, -SO₂—C₁—C₆-alkyl, -SO₂—Ar, -SO₂—C₁—C₆-alkoxy, -SO₂—OAr, -SO₂—NH₂, -SO₂—NH—C₁—C₆-alkyl, -SO₂—N(C₁—C₆-alkyl)₂, -SO₂—NHAr, -SO₂—C₁—C₆-alkoxy;
- n is 0 or 1;
 or a pharmaceutically acceptable salt thereof.

2. A method according to Claim 1 wherein the anxiety disorder is selected from the group of anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia or specific phobias
3. A method according to Claim 1 or Claim 2 in which the compound of formula (I) is selected from the group of:
- 2-Amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino benzene;
- 2-Amino-4-(4-trifluoromethylbenzylamino)-1-ethoxycarbonylamino benzene;
- 2-Amino-4-benzylamino-1-ethoxycarbonylamino benzene;
- 2-Amino-4-(3,5-dichlorobenzylamino)-1-ethoxycarbonylamino benzene;
- 2-Amino-4-(3,5-dichlorobenzylamino)-1-propyloxycarbonylamino benzene;
- 2-Amino-(2-chlorobenzylamino)-1-(diethylcarbamoylamino) benzene;
- 2-Amino-4-(2,4-dichlorobenzylamino)-1-(dimethylcarbamoylamino) benzene; or
- 1,2-Diacetylamino-4-(4-fluorobenzylamino) benzene;
- or a pharmaceutically acceptable salt thereof.
4. A method according to Claim 1 or Claim 2 in which the compound of formula (I) is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid or a pharmaceutically acceptable salt or ester form thereof.
5. A method according to Claim 4 in which the compound of formula (I) is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester or a pharmaceutically acceptable salt form thereof.
6. A method according to any one of Claims 1 to 5 wherein the mammal is a human.
7. Use of a compound of formula (I) as defined in Claim 1 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment or inhibition of anxiety disorders in a mammal.

8. Use according to Claim 7 wherein the anxiety disorder is selected from the group of anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia or specific phobias.

9. Use according to Claim 7 or Claim 8 in which the compound of formula (I) is one of the following:
2-Amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino benzene;
10 2-Amino-4-(4-trifluoromethylbenzylamino)-1-ethoxycarbonylamino-benzene;
2-Amino-4-benzylamino-1-ethoxycarbonylamino-benzene;
2-Amino-4-(3,5-dichlorobenzylamino)-1-ethoxycarbonylamino benzene;
2-Amino-4-(3,5-dichlorobenzylamino)-1-propyloxycarbonylamino benzene;
2-Amino-(2-chlorobenzylamino)-1-(diethylcarbamoylamino) benzene;
15 2-Amino-4-(2,4-dichlorobenzylamino)-1-(dimethylcarbamoylamino) benzene; or
1,2-Diacetylamino-4-(4-fluorobenzylamino) benzene;
or a pharmaceutically acceptable salt thereof.

10. Use of N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid or a pharmaceutically acceptable salt or ester form thereof in the preparation of a medicament for the treatment or inhibition of anxiety disorders in a mammal.

11. Use according to Claim 10 wherein the compound is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester or a pharmaceutically acceptable salt form thereof.

12. Use according to Claim 10 or 11 wherein the anxiety disorder is selected from the group of anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia and specific phobias.

13. Use according to any one of Claims 7 to 12 wherein the mammal is a human.

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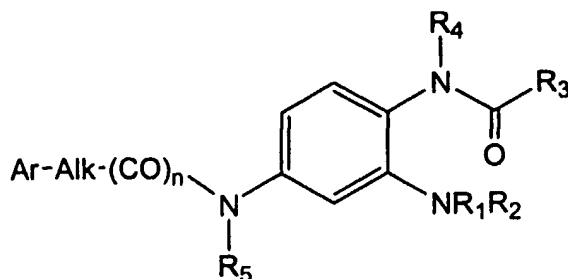
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(54) Title: METHODS OF TREATING ANXIETY DISORDERS



(I)

(57) Abstract: This invention provides methods for treating, preventing or inhibiting anxiety, anxiety-related conditions and phobias in a mammal using compounds of the formula (I) wherein: R₁ is H, alkyl, alkanoyl or the radical Ar; R₂ is H or alkyl; R₃ is alkoxy, NH₂, alkylamino, dialkylamino, amino substituted by the radical Ar, alkyl, alkenyl, alkynyl, or the radicals Ar or ArO-; R₄ is H, alkyl or the radical Ar; R₅ is H or alkyl or the radical Ar; or a pharmaceutically acceptable salt or ester form thereof; Ar is an

optionally substituted phenyl radical; and n is 0 or 1, or a pharmaceutically acceptable salt or ester form thereof, with the methods particularly including the use of N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester, also known as retigabine.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/27 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | US 5 384 330 A (DIETER HANS-REINHOLD ET AL) 24 January 1995 (1995-01-24) cited in the application claims 1-5 | 1-13 |
| A | US 5 849 789 A (BARTSCH RENI ET AL) 15 December 1998 (1998-12-15) cited in the application column 1; claims 1-4 | 1-13 |
| A | US 5 852 053 A (BARTSCH RENI ET AL) 22 December 1998 (1998-12-22) cited in the application column 1; claims 1-14 | 1-13 |
| | -/-- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 July 2002

Date of mailing of the international search report

30/07/2002

Name and mailing address of the ISA

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Authorized officer

Kling, I

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | <p>US 6 117 900 A (DOST RITA ET AL) 12 September 2000 (2000-09-12) cited in the application column 6, line 6 -column 8, line 37; claims 1-8</p> <p>---</p> | 1-13 |
| A | <p>RUNDFELDT C: "CHARACTERIZATION OF THE K+ CHANNEL OPENING EFFECT OF THE ANTICONVULSANT RETIGABINE IN PC12 CELLS" EPILEPSY RESEARCH, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 35, no. 2, June 1999 (1999-06), pages 99-107, XP000972218 ISSN: 0920-1211 abstract</p> <p>---</p> | 1-13 |
| A | <p>RUNDFELDT C ET AL: "THE NOVEL ANTICONVULSANT RETIGABINE ACTIVATES M-CURRENTS IN CHINESE HAMSTER OVARY-CELLS TRANFECTED WITH HUMAN KCNQ2/3 SUBUNITS" NEUROSCIENCE LETTERS, LIMERICK, IE, vol. 282, no. 1/2, 17 March 2000 (2000-03-17), pages 73-76, XP000972246 ISSN: 0304-3940 abstract</p> <p>---</p> | 1-13 |
| P,X | <p>WO 01 01970 A (COX BRIAN ;DUPERE JOSEPH (GB); GLAXO GROUP LTD (GB); BURBIDGE STEP) 11 January 2001 (2001-01-11) page 1, line 6 -page 6, line 9; claims 1-8</p> <p>-----</p> | 1-13 |

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| US 5384330 | A | 24-01-1995 | DE 4200259 A1 | 15-07-1993 |
| | | | AT 134611 T | 15-03-1996 |
| | | | CA 2086654 A1 | 09-07-1993 |
| | | | DE 59205496 D1 | 04-04-1996 |
| | | | DK 554543 T3 | 18-03-1996 |
| | | | EP 0554543 A2 | 11-08-1993 |
| | | | ES 2084914 T3 | 16-05-1996 |
| | | | GR 3019653 T3 | 31-07-1996 |
| | | | JP 3145220 B2 | 12-03-2001 |
| | | | JP 5345752 A | 27-12-1993 |
| | | | MX 9300014 A1 | 01-07-1993 |
| | | | SG 48046 A1 | 17-04-1998 |
| | | | ZA 9300011 A | 05-08-1993 |
| US 5849789 | A | 15-12-1998 | DE 19539861 A1 | 30-04-1997 |
| | | | AT 178487 T | 15-04-1999 |
| | | | AU 706735 B2 | 24-06-1999 |
| | | | AU 1540097 A | 15-05-1997 |
| | | | BR 9610899 A | 13-07-1999 |
| | | | CA 2188841 A1 | 27-04-1997 |
| | | | CZ 9801225 A3 | 16-09-1998 |
| | | | WO 9715300 A2 | 01-05-1997 |
| | | | DE 59601624 D1 | 12-05-1999 |
| | | | EP 0857065 A2 | 12-08-1998 |
| | | | ES 2131973 T3 | 01-08-1999 |
| | | | GR 3030336 T3 | 30-09-1999 |
| | | | HU 9900508 A2 | 28-06-1999 |
| | | | JP 11515007 T | 21-12-1999 |
| | | | NO 981503 A | 02-04-1998 |
| | | | NZ 326754 A | 27-03-2000 |
| | | | PL 325956 A1 | 17-08-1998 |
| | | | SK 52098 A3 | 09-09-1998 |
| | | | TW 457084 B | 01-10-2001 |
| | | | US 5852053 A | 22-12-1998 |
| | | | ZA 9608991 A | 10-06-1997 |
| US 5852053 | A | 22-12-1998 | DE 19539861 A1 | 30-04-1997 |
| | | | AT 178487 T | 15-04-1999 |
| | | | AU 706735 B2 | 24-06-1999 |
| | | | AU 1540097 A | 15-05-1997 |
| | | | BR 9610899 A | 13-07-1999 |
| | | | CA 2188841 A1 | 27-04-1997 |
| | | | CZ 9801225 A3 | 16-09-1998 |
| | | | WO 9715300 A2 | 01-05-1997 |
| | | | DE 59601624 D1 | 12-05-1999 |
| | | | EP 0857065 A2 | 12-08-1998 |
| | | | ES 2131973 T3 | 01-08-1999 |
| | | | GR 3030336 T3 | 30-09-1999 |
| | | | HU 9900508 A2 | 28-06-1999 |
| | | | JP 11515007 T | 21-12-1999 |
| | | | NO 981503 A | 02-04-1998 |
| | | | NZ 326754 A | 27-03-2000 |
| | | | PL 325956 A1 | 17-08-1998 |
| | | | SK 52098 A3 | 09-09-1998 |
| | | | TW 457084 B | 01-10-2001 |
| | | | US 5849789 A | 15-12-1998 |
| | | | ZA 9608991 A | 10-06-1997 |

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---------------------|----------------------------|------------|---------------------|
| US 6117900 | A | 12-09-2000 | AU | 7906100 A | 30-04-2001 |
| | | | BR | 0014293 A | 21-05-2002 |
| | | | WO | 0122953 A2 | 05-04-2001 |
| | | | NO | 20021418 A | 21-03-2002 |
| WO 0101970 | A | 11-01-2001 | AU | 5557700 A | 22-01-2001 |
| | | | EP | 1207863 A2 | 29-05-2002 |
| | | | WO | 0101970 A2 | 11-01-2001 |